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EXAMINER	
RAE, CHARLESWORTH E	

ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,278	HOSSAINY ET AL.	
	Examiner	Art Unit	
	CHARLESWORTH RAE	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 September 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *14-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/08/04;06/13/05;09/09/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's arguments, filed 09/29/08, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Status of the Claims

Claims 1-11, 13-27 are currently pending in this application.

Claims 14-26 are withdrawn for being directed to non-elected subject matter.

Claims 1-11, 13, and 27 are under examination.

Claim Amendment

Applicant's amendment, received 09/29/08, is acknowledged.

Information Disclosure Statement

In response to applicant's request for an initialed copy of the IDS dated March 4, 2004, and June 9, 2005, it is noted that initialed copies of the requested IDS are being provided as attachments. The examiner regrets the fact applicant did not receive said initialed copies with the prior Office action.

Clarification

Applicant's statement pointing out the inadvertent error regarding the statement "Smith et al. do not teach applicant's elected embodiment "c" of Polyactive polymer-diazenium diolated conjugate," is acknowledged (see

applicant's Response, received 09/29/08, page 11, 4th para.). The Office action is hereby amended to clarify the record that applicant's elected biobeneficial polymer is the polymer of claim 11 where R is H poly(ester amide) as evidenced by applicant's Response, received 04/27/07, page 10, lines 4-7. Further, applicant's attention is specifically drawn to page 5 of the Office action, mailed 07/22/08, lines 1-8, where the examiner correctly indicates that the polymer having the general formula recited in claim 11, wherein R is H, is the elected beneficial polymer species. Thus, the error discussed above was clearly inadvertent and therefore do not materially affect the merits of the rejection.

Response to applicant's arguments/remarks

Lack of written description rejection under 112, 1st paragraph

This rejection is withdrawn in view of the claim amendment.

Rejection under 112, 2nd para.

This rejection is withdrawn in view of applicant's claim amendment.

Rejection under 102(b)

This rejection is withdrawn in view of applicant's claim amendment.

REJECTIONS

Claim rejections – 35 USC 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 10, and 13, are rejected under 103(a) as being unpatentable over Llanos et al. (US Patent Publication No. 2002/0094440 A1; already made of record), in view of Waugh et al. (US Patent Application Pub. No. 2004/0072857), in further view of Chen et al. (US Patent Application Pub. No. 2004/0001889), and as evidenced by Wikipedia.

Llanos et al. (US Patent Publication No. 2002/0094440 A1) **biocompatible polymer coating compositions for coating implantable medical devices**, including stents, wherein said coating compositions are present on the surface of said device, wherein said surface is an inert surface to be in contact with body tissue of a mammal upon implantation of said device in said mammal (abstract; para. 0003-0004; and 0010). Llanos et al. teach that even though stents are commonly used in transluminal procedures such as angioplasty to restore adequate blood flow to the heart and other organs, deployment of stents may stimulate foreign body reactions that result in thrombosis or restenosis (para. 0044). Llanos et al. teach coating compositions comprising a film-forming **polyfluoro copolymer** containing the polymerized residue of a moiety selected from the group consisting of vinlyidenefluoride and tetrafluoroethylene copolymerized with a second moiety other than the first moiety (abstract; para. 0010). Llanos et al. teach that bioabsorbable and biostable stent coating compositions generally comprise polymeric coatings that either encapsulate a pharmaceutical/ therapeutic agent (**e.g. taxol and rapamycin**) or bind such agent to the surface (e.g. heparin coated stents). See paras. 0006 and 0044-0047). Llanos et al. exemplify a stent coating composition comprising rapamycin and poly (VDF/HFP). See paras. 0014; 0030, 0044-0049, and Figure 4). Llanos et al. also exemplify coating compositions comprising polymer blends comprising a poly (VDF) homopolymer (= Solef 1008) and polyfluoro copolymers of poly (VDF/HFP), or Solef 11010 and 11008 (page 5, para 0039). Llanos et al. teach the instant claimed limitation "a." Specifically, Llanos et al. teach implantable medical devices, including stents, and biocompatible coating

compositions for use on said implantanble medical devices, wherein said coatings comprise a film-forming polyfluoro copolymer comprising the polymerized residue of a first moiety selected from the group consisting of vinylidenefluoride (VDF) and tetrefluoroethylerne (TFE), and the polymerized residue of a second moiety other than said first moiety and which is copolymerized with said first moiety; the second moiety being capable of providing toughness or elastomeric properties to the polyfluoro copolymer (paras. 0010; 0015). Llanos et al. exemplify a coating composition comprising Solef, which is applicant's elected fluorinated polymer (page 5, Example 1; see also instant specification, page 1, para. 0015). Also, Llanos et al. also exemplify a coating comprising biologically active agents; namely, a polymeric coating composition comprising poly (VDF/HFP) and rapamycin (page 5, Example 3).

Although Llanos et al. teach implantable (e.g. stent) coating compositions comprising applicant's elected fluoropolymer species (i.e. Solef) and rapamycin, this reference does not teach coating compositions wherein the therapeutic agent (e.g. rapamycin) is conjugated specifically to instantly claimed biologically beneficial polymer (polyester amides).

Waugh et al. (US Patent Application Pub. No. 2004/0072857) teach improved compositions and methods for their preparation and use for coating medical devices (e.g. stents, grafts, other vascular prostheses), wherein said compositions comprise linked pluralities of molecules which specifically bind to the mammalian target of rapamycin (mTOR), including **rapamycin (sirolimus)**, CCI-779, RAD-001, SDZ Rad (**Everolimus**), tacrolimus (FK506), pimecrolimus (ASM 981; see abstract; and paras.

0012-0015, 0022, and 0037- 0039). In particular, Waugh et al. teach compositions comprising derivatized rapamycin, wherein rapamycin is bonded to a polymer backbone **either covalently or non-convalently**, for application to vascular prostheses and other implantable devices to inhibit hyperplasia or for other therapeutic purposes (abstract; and Figure 4). Waugh et al. teach that suitable polymers include poly (amino acids), polyalcohols, polyamines, hydroxyaliphatic carboxylic acids, and other homo and copolymers with active side chains, such as carboxylates, amines, hydroxyls (para. 0020). Waugh et al. exemplify rapamycin-polymer conjugates wherein the rapamycin is linked to the **polymer via NH-C=0 linkage** (see abstract; paras. 0037-0039; and Figures 9-11). Waugh et al. also exemplify rapamycin-polymer conjugates, wherein the rapamycin is linked to the **polymer via a O-C=O linkage** (Figures 15 and 16). Waugh et al. teach suitable polymer backbones, including poly (amino acids), polyamines, and homo or copolymers with active side chains, such as carboxylates, amines, and hydroxyls, may serve as binding moities (para. 0015, lines 10-16; see also Figures 9-11, and 15-16). Waugh et al. teach rapamycin—PEG conjugates (paras. 0048-0050). Waugh et al. also teach polylysine amide-ester linked rapamycin, wherein the free amines of polylysine are reacted with the free hydroxyl at position 42 of rapamycin using carbonic acid or bicarbonate (para. 0048). Waugh et al. state that it is desirable to polymerize or link rapamycin or related drugs to a backbone polymer in order to enhance the amounts of drug available on the surface of the prosthesis (para. 0009, lines 9-14).

Chen et al. (US Patent Application Pub. No. 2004/0001889) is added to show the general state of the art regarding bioerodible, biocompatible polymers ((paras 0094-0095; 0142; and 0148). Chen et al. teach that bioerodable, biocompatible polymers, including chitosan, PEG, PEA, poly(amino acids), hyaluronic acid, terpolymers and mixtures thereof generally degrade via hydrolysis. Chen et al. teach the release profile of the composition comprising these polymers, when used as drug carriers, depends on the degradation rate of the polymer (paras 0094-0095; 0142; and 0148).

Wikepedia as added only as an evidentiary reference to show that lysine has NH2 and OH-C=O moieties, which are capable of forming amide-ester links with rapamycin (page 1).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references by using any suitable biodegradable biologically beneficial polymer (e.g. PEG, or lysine), including applicant's claimed poly(ester amide) polymers, as a carrier to deliver a biologically active agent (e.g. rapamycin), wherein the biologically beneficial polymer is conjugated to said biologically active agent (e.g. PEG-rapamycin, or polylysine-rapamycin) as taught by Waugh et al. for use in the implantable coating composition comprising a fluorinated polymer (e.g. Solef) as taught by Llanos et al. to control the drug release properties of the coating composition. One would have been motivated to do so because Waugh et al. suggest that it is desirable to link rapamycin and related drugs to a biodegradable polymer backbone in order to enhance the amounts of rapamycin and related drugs on the surface of prosthetics (e.g. stent) and Chen et al. teach that bioerodable,

biocompatible polymers (e.g. PEG, PEA, poly (amino acids), hyaluronic acid) when used as drug delivery carriers affect the release profile of the composition, depending on the degradation rate of bioerodable/biodegradable polymer used (paras 0094-0095; 0142; and 0148). Further, both Llanos et al. and Waugh et al. teach coating compositions for coating implantable medical devices (e.g. stent) comprising rapamycin

To the extent that both the instant application and Waugh et al. teach PEG-rapamycin conjugate, one would reasonably expect to also conjugate rapamycin with any suitable biodegradable polymer (e.g. lysine), including the instant claimed biologically beneficial polymers, since Waugh et al. suggest that rapamycin may be covalently bound to biodegradable backbone polymers and polylysine as taught by Waugh et al. is biodegradable and is capable of interacting with rapamycin to create poly(ester amide) bonds in view of its chemical structure as evidenced by the above referenced teaching of Waugh (para. 0048) and Wikepedia.

Further, it would have been obvious to a person of skill in the art at the time the invention was made to substitute a PEG beneficial polymer as taught by Waugh et al. with a PEA beneficial polymer as taught by Chen et al. to conjugate the biologically active agent (e.g. rapamycin). One would have been motivated to do so because Chen et al. suggest that PEG and PEA polymers are functionally equivalent biodegrable polymers for use as drug carriers (paras. 0094-0095; 0142; and 0148). Thus, one would have expected to substitute PEG as taught by Waugh et al. with any suitable PEA species, including applicant's elected PEA species, for use as a carrier for a

biologoically active agent (e.g. rapamycin) since lysine as taught by Waugh et al. is also capable of forming conjugates with rapamycin (para. 0048).

It is noted that applicant teaches that the term ""conjugated" is defined as "linked," for example, covalently lined. The term "conjugation" is defined as a process of forming a link, for example, a covalent link. See specification, page 7, lines 9-10. Thus, the term "conjugated" given its broadest reasonable possible interpretation in light of the specification is not limited to covalently bonded drug-polymer complexes i.e. it also encompasses non-covalently linked drug-polymer complexes as well.

It is noted that the term "a coating disposed on at least a portion" as recited in claim 1 overlaps with the prior art since the prior art teaches coated implantable devices and the term "at least a portion" only requires that the device be coated.

With respect to the term "wherein the implantable medical device is a stent," it is noted that Llanos et al. also teach stents (para. 0044).

With respect to instant claimed "component (a)," it is noted that Llanos et al. teach stent coating compositions comprising applicant's elected fluorinated polymer species (= Solef). Thus, Solef as taught by the prior art reads on the "component a" with respect to claims 1, and 3-6.

With respect to the product by process limitations recited in claims 3-5 regarding "component a," it is noted that the prior art teaches applicant's elected "component a." To the extent that the prior art teaches the identical instant claimed fluorinated polymer species (Solef), the process of preparing Solef is not found to provide structure to the

composition because (Solef) as taught by the prior art is capable of performing the intended function.

It is noted that rapamycin as taught by the prior art reads on claim 13 because claim 13 also recites "rapamycin."

It is noted that the instant application discloses that the term **"poly (ester amide)"** is defined as a polymer having at least one ester fragment (**I**) represented by O-C=O and at least one amide fragment (**II**) represented by –NH-C=O (page 7, lines 17-25). Thus, the poly(ester amides) as taught by Waugh et al. overlaps with the instant claimed "poly(ester amide)" as recited in **claims 1 and 7**, and the term *"wherein poly(ester amides) include polymers having at least one ester bond and at least one amide bond"* as recited in **claim 8**. Further, since Waugh et al. teach rapamycin-polymer conjugates, including rapamycin-lysine conjugates (para. 0048), wherein the rapamycin is linked to the **polymer via NH-C=0 linkage** and **via a O-C=O linkage,** and since lysine chemical structure is comprised of an NH2 terminus and a HO-C=O terminus, one would reasonably expect that the rapamycin-polylysine conjugate would also have O-C=O and NH-C=O moieties present following conjugation absent evidence to the contrary.

With respect to the product by process limitation recited in claim 10, to the extent that the prior art teach poly(ester amide)-drug conjugates, for the reasons discussed above in connection with claims 7, and 8, the process by process limitation recited in claim10 is not found to provide structure to the instant claimed composition because

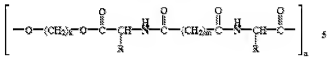
poly(ester amide)-drug conjugates as taught by the prior art are capable of performing the intended function.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Claims 9 and 11 are rejected under 103(a) as being unpatentable over Llanos et al. (US Patent Publication No. 2002/0094440 A1; already made of record), in view of Waugh et al. (US Patent Application Pub. No. 2004/0072857), in further view of Chen et al. (US Patent Application Pub. No. 2004/0001889), Katsarava et al. (US Patent 6,703,040) and Molnar-Kimber et al. (US Patent 6,324,970), and as evidenced by Wikipedia).

The above discussions of Llanos et al and Waugh et al. are incorporated by reference. These references do not teach the specific instantly claimed poly(ester amide) polymer species. However, Waugh et al. teaches polylysine with amide-ester linked rapamycin (para. 0048), which is encompassed by the genus of "poly (ester) amide" as defined by applicant (specification, page 7, lines 17-25).

Katsarava et al. (US Patent 6,703,040) teach bioerodable polymer cojnstruct drug delivery systemsto provide controlled release of bioactive materials comprising poly (ester-amide) polymers (PEA) (abstract). In particular, Katsarava et al. teach poly (ester-amides) that are non-toxic, wherein compounds having the below structure are preferred (col. 3, lines 1-23; and col. 5, lines 1-10;).



where
k=2–12, especially 2, 3, 4, or 6,
m=2–12, especially 4 or 8, and
R=$CH(CH_3)_2$, $CH_2CH(CH_3)_2$, $CH(CH_3)CH_2CH_3$, (CH_2)
$_3CH_3$, $CH_2C_6H_5$, or $(CH_2)_3SCH_3$.

Katsarava et al. teach PEA polymer blend may be used to provide a bioerodible coating on a support material which may or may not be biodegradable, including indwelling catheters, and any other appliances that are in contact with body cavities, the blood circulation, or the lymphatic circulation (col. 6, lines 34-65; col. 7, lines 1-22). Katasarava et al. teach that bioactive and inactive biocompatible materials may be included in the erodable polymeric construct, including **antineoplastic agents** (col. 7, lines 23-49, especially lines 32-33). In particular, Katasarava et al. teach naturally occurring biodegradable poly(ester amides) that are non-toxic and methods of synthesizing said non-toxic naturally occurring biodegradable polymers (col. 4, line 52 to col. 5, line 3).

Although Katsarava et al. teach PEA polymers that overlap with the instant claimed PEA polymers (e.g. lysine), this reference does not teach the instant claimed poly(ester amides) having the specific linking groups recited in claim 9.

Molnar-Kimber et al. (US Patent 6,324,970) is added to show the general state of the art regarding the use of linking groups to prepare drug-conjugates. Molnar-Kimer teach that rapamycin conjugates may be prepared in such ways as to encompass a wide range of linking groups and terminal functional groups, wherein the linking groups

may be linear or branched alkylenes comprising from 1 to 15 atoms (e.g. substituted or unsubstituted methylene, ethylene, n-propylene, iso-propylene, n-butylene groups, and wherein the substituted group may be substituted with e.g. substitute carboxyls such as esters, amides, and substituted amides (col. 2, line 23 to 3, line 35). The linking group (L) can also contain or consist of substituted or unsubstituted aryl, aralkyl, or heteroaryl groups (col. 3, lines 19-35). Molnar-Kimber et al. teach that **the choice of linking group (L) is not critical** and may be selected by one of ordinary skill taking normal precautions to assure that stable compounds are produced (col. 3, lines 31-35).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references by substituting the polymer backbone as taught by Waugh et al. with the polymer backbone as taught by Katasarava et al. to bind the biologically active agent (e.g. rapamycin) in order to control the drug release characteristics of the composition as taught by Llanos et al. One would have been motivated to use a poly(ester amide) taught by Katasarava et al. to bind rapamycin as taught Waugh et al. because Katasarava et al. suggest that bioerodible amino acid poly (amide ester) polymer can be used to prepare controlled release polymer-drug coating composition for coating implantable medical devices (e.g. indwelling catheters; col. 2, lines 39-49) and Waugh et al. also teach PEA-polymer(e.g. polylysine)-antineoplastic agent (e.g. rapamycin) conjugates, wherein the PEA-polymer serves as a carrier molecule for delivering the antineoplastic agent to the targeted site of action

Further, it would have been obvious to a person of skill in the art at the time the invention was made to combine the teachings of the cited references by manipulating the length of PEA polymer backbone of the bioerodible/biocompatible polymers (e.g. lysine) as taught by Katsarava et al. by adding any suitable inactive linking group, including the instant claimed linking groups (M and P) as recited in instant claim 9, to increase the length of the polymeric backbone of the bioerodable/biocompatible polymer to which the rapamycin is bound, in order to extend the drug release properties of the coating composition (= controlled release composition). One would have been motivated to do so because Katsarava et al. suggest that any inactive biocompatible material may be included in the bioerodable polymeric construct for use in conjugating antineoplastic drugs (e.g. rapamycin) present in coating compositions for coating implantable medical devices (e.g. stents), which would reasonably increase the length of the polymer backbone and extend the time need to degrade said polymer (= extend the duration of drug released from the drug-polymer construct), as well as alter the drug characteristics of the composition since added chain length would reasonably require a longer time to be degraded as evidenced by the teaching of Molnar-Kimber et al. that **the choice of linking group (L) is not critical** and may be selected by one of ordinary skill taking normal precautions to assure that stable compounds are produced (col. 3, lines 31-35).

With respect to claim 11, it is noted that the preferred poly (ester-amide) compounds taught by Katsarava et al. overlap with the general formula recited in instant

claim 11, wherein reference m (= instant y) is 2-12, reference k (= instant x) is 2-12, reference R is isopropyl, or iso-butyl, sec-butyl, and benzyl (i.e. instant R = iso-propyl, iso-butyl, sec butyl, iso-butyl, and benzyl; col. 3, lines 1-12).

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Claim 27 is rejected under 103(a) as being unpatentable over Llanos et al. (US Patent Publication No. 2002/0094440 A1; already made of record), in view of Waugh et al. (US Patent Application Pub. No. 2004/0072857), and Smith et al. (US Patent 6,451,337), and as evidenced by Wikipedia.

The above discussions of Llanos et al and Waugh et al. are incorporated by reference. These referenced do not teach diazenium diolates or diazenium diolate covalently bonded to the specific instantly claimed biologically beneficial polymer.

Smith et al. (US Patent 6,451,337) teach polymeric coating compositions for use in implantable medical devices such as stents comprising polymeric conjugates of diazenium diolates, wherein said diazenium diolates possess beneficial properties (col. 3, lines 63 to col. 4, lines 3; col. 13, lines 62-67; and reference claims 6, 13-14). Smith et al. disclose that there remains a great need to develop a low cost, readily **biodegradable, biocompatibl**e nitric oxide donor polymer composition comprising a nitric oxide dimer and a medically beneficial carrier molecule capable of improved site specific delivery and controlled release of nitric oxide (NO) to target tissues under

physiological conditions, without the further side effects of the nitric oxide donor compounds (col. 3, lines 63 to col. 4, lines 3). Smith et al. teach a chitosan-based polymeric composition capable of site specific delivery and controlled release of nitric oxide to target tissues comprising a modified chitosan polymer and a nitric oxide dimer, wherein the nitric oxide dimer is covalently bound to the modified chitosan polymer, forming a diazenium diolate (NONOate) derivative of the modified chitosan polymer (col. 6, lines 21-31). Smith et al. discloses that the chitosan-based nitric oxide donor composition has first order nitric oxide release kinetics and provides site specific delivery and controlled release of nitric oxide under physiological conditions (col. 4, lines 51-62; col. 13, lines 11-41). Smith et al. teach that chitosan-based NONOate compositions wherein the composition further comprises a medically beneficial carrier (col. 8, lines 16-20). Smith et al. disclose that chitosan-based NONOate composition may be coated onto stents and implants useful for inhibition of platelet aggregation and adhesion to blood vessel walls following medical procedures (col. 13, lines 60-67).

It would have been obvious to a person of skill in the art at the time the invention was made to combine the cited references by substituting PEG-rapamycin as taught by Waugh et al. with the diazenium diolate-biodegrable polymer conjugate as taught by Smith et al., including applicant's claimed diazenium diolates-biologically beneficial polymer conjugates, for use in the implantable device coating composition as taught by Llanos et al. to treat a nitric oxide associated condition (abstract; col. 6, line 20 to col. 7, line 15). One would have been motivated to do so because Smith et al. suggest that diazenium diolate may be conjugated with any suitable biodegrable polymer carrier to

deliver drugs to specific sites in the body to treat conditions wherein a NO donor is the preferred treatment and the biologically beneficial polymers as taught by the prior art and the instant claimed biologically beneficial polymers are also biodegradable polymers that are used to deliver drugs. Besides, Smith suggest that there is a great need for medically beneficial carrier molecule capable of improved site specific delivery and controlled release of nitric oxide (NO) to target tissues under physiological conditions, without the further side effects of the nitric oxide donor compounds. Thus, one would reasonably expect that the genus of diazenium diolate-biodegradable polymer conjugates, including applicant's claimed diazenium diolates-polymer conjugate compounds, to exhibit similar binding properties absent evidence to the contrary.

Thus, it would have been obvious to a person of skill in the art at the time the invention was made to create the instant claimed invention with reasonable predictability.

Response to applicant's arguments/remarks

Applicant's arguments are rendered moot by the new basis this rejection. However, the merits of the above cited references (Llanos et al. and Smith et al.) are maintained for the reasons discussed above.

In response to applicant's argument that Smith et al. does not teach a medical device having a bioactive agent conjugated to a polymer, the examiner wishes to point out that Smith et al. do teach a chitosan-based polymeric composition capable of site specific delivery and controlled release of nitric oxide to target tissues comprising a modified chitosan polymer and a nitric oxide dimer, wherein the nitric oxide dimer is

covalently bound to the modified chitosan polymer, forming a diazenium diolate (NONOate) derivative of the modified chitosan polymer (col. 6, lines 21-31). Further, since chitosan polymer is a biodegradable polymer and Smith suggest that there is a great need for medically beneficial carrier molecule capable of improved site specific delivery and controlled release of nitric oxide (NO) to target tissues under physiological conditions, without the further side effects of the nitric oxide donor compounds, one would be motivated to use any suitable biodegradalbe polymer, including applicant's elected biobeneficial polymer, to conjugate the diazenium diolate as taught by the prior art to improve the site specific delivery of the diazenium diolate and/or provide a controlled release drug delivery coating composition comprising the diazenium diolate – biodegradable polymer conjugate absent evidence to the contrary. In addition, it is noted that applicant teaches that the term ""conjugated" is defined as "linked," for example, covalently lined. The term "conjugation" is defined as a process of forming a link, for example, a covalent link (specification, page 7, lines 9-10). Thus, the term "conjugated" given its broadest reasonable possible interpretation in light of the specification is not limited to covalently bonded drug-polymer complexes i.e. it also encompasses non-covalently linked drug-polymer complexes as well.

With respect to applicant's argument that Llanos does not disclose a biobeneficial polymer-bioactive agent conjugate, it is noted that Llanos et al. provides a general teaching that bioabsorbable and biostable stent coating compositions generally comprise polymeric coatings that either encapsulate a pharmaceutical/ therapeutic

agent (**e.g. taxol and rapamycin**) or bind such agent to the surface (See paras. 0006 and 0044-0047), which provides a general teaching Llanos et al. exemplify a stent coating composition comprising rapamycin and poly (VDF/HFP). See paras. 0014; 0030, 0044-0049, and Figure 4). To the extent that Llanos et al. teach coating compositions comprising polymer blends bound to active agents, wherein the biodegradable polymer backbone (e.g. PEG) utilized to bind the active agent (e.g. rapamycin) overlap with the instant claimed biologically beneficial polymers and biologically active agents, one would reasonably expect that the binding characteristic between the therapeutic agent and polymer encompassed by the prior art would ecovalent and non-covalently bonded therapeutic agent-polymer moieties depending on the specific chemical structure of the therapeutic agent and the polymer to which the therapeutic agent is bound absence evidence to the contrary.

Relevant Art of Record

The below art made of record and relied upon are considered pertinent to applicant's invention.

Davila et al. (US Patent 7,056,550; already made of record) teach a medical device for implantation into a treatment site of a living organism comprising a biocompatible vehicle affixed to at least a portion of the medical device, and at least one agent in therapeutic dosages incorporated into the biocompatible vehicle (col. 5, lines 24-53). Davila et al. exemplify a polyfluroro copolymer (Solef 21508) coating.

Fitzhugh et al. (US Patent 6,270,779) teach biocompatible metallic medical devices having silanized surfaces coupled to nucelophile residues that release sustained, therapeutic amounts of nitric oxide to specific sites within a mammalian body, wherein the biocompatible metallic medical device can be provided with anti-thrombogenic, lubricuous coatings that release sustained, therapeutic amounts of nitric oxide (abstract). NO's directly cytotoxic/cytostitc properties may sognificantly reduce vascular smooth muscle cell proliferation and help restenosis (col. 2, lines 1-5). Fitzhugh et al. propose metallic stents having drug releasing polymeric coatings (col. 6, lines 1-7). Fitzhugh et al. teach that polymeric stents present many unsolved challenges (col. 6, lines 7-13). Fitzhugh et al. disclose that arterial stents have been fabricated from a variety of compounds, including metals and biocompatible synthetic polymers (e.g. polypropylene, polyethylene, polyesters, polyethers, polyurethanes and polylactides). Fitzhugh et al. teach medical devices for delivering nitric oxide in therapeutic concentrations for sustained periods of time comprising: metallic surfaces having nitric oxide releasably bound thereto through diazeniumdiolated nucleophiles coupled to silane intermediates, said silane intermediates being bound to said metallic surface.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila G. Landau, can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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28 December 2008

/C. R./

Examiner, Art Unit 1611

/Sharmila Gollamudi Landau/

Supervisory Patent Examiner, Art Unit 1611